

REMARKS

Claims 1-56 constitute the pending claims in the present application, prior to Amendment. Claim 43 is currently under consideration. Applicants cancel, without prejudice, claims 44-56. Applicants note that claims 44-56 were withdrawn from consideration as being directed to a nonelected invention. Applicants reserve the right to prosecute claims of similar or differing scope in this or future applications.

Claim 43 has been amended to more particularly point out certain embodiments of Applicants' invention. Support for Applicants' amendment is found throughout the specification. Specific support can be found, for example, in paragraphs [0042], [0053], and [0118] of the published specification. No new matter has been entered.

Applicants add new claims 57-68. Support for the subject matter of the newly added claims is found throughout the specification. Specific support can be found, for example, in paragraphs [0042], [0053], and [0118] of the published specification. No new matter has been entered. Applicants note that claims 64-68 are means-plus-function claims presented in compliance with 35 U.S.C. § 112, sixth paragraph.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Specification

The title was objected to for allegedly failing to be adequately descriptive of the claimed invention. Applicants traverse. Nevertheless, to expedite prosecution, Applicants have amended the title to provide a title that is clearly indicative of the presently claimed invention. Applicants' amendment to the title is believed to obviate the objection.

The disclosure is objected to because Applicants' priority statement did not indicate that application number 09/021660 has issued as U.S. Patent No. 6713065. Applicants' amendment to the first paragraph of the specification is believed to obviate the objection.

The disclosure is objected to because certain portions of the Brief Description of the Figures omitted reference to each part of the figures. Applicants' amendments to the Brief Description of the Figures are believed to obviate the objection.

In view of Applicants' amendments to the specification, reconsideration and withdrawal of the objections to the specification are requested.

Claim Rejection – 35 U.S.C. § 112, first paragraph, enablement

Claim 43 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

In evaluating the enablement of the claimed subject matter, both the courts and the MPEP have acknowledged that some experimentation is permissible, as long as that experimentation is not undue (MPEP 2164.04). “An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance.” *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). However, the courts have been clear that the determination of whether undue experimentation is required should not be made based solely on the time and cost involved in conducting such experimentation. “The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). “Time and expense are merely factors in this consideration and are not the controlling factors.” *United States v. Telecommunications Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989).

Applicants contend that the specification and the art provide extensive guidance such that one of skill could practice the claimed invention without undue experimentation. The level of skill in the art is very high, the specification and art provided extensive guidance concerning the functional and structural characteristics of the compounds for use in the claimed methods, and the specification and the art provided extensive guidance concerning vasculogenesis and angiogenesis. As such, Applicants submit that one of skill in the art would expect to expend no more effort than is reasonably undertaken in the art to practice the invention.

Additionally, Applicants note that the state of the art since the effective filing date of the instant application supports Applicants' contention that the claimed invention is enabled throughout its scope based on the specification and level of skill in the art. Applicants direct the Examiner's attention to a few examples from the post-filing literature (Pola et al., 2001; Pola et al., 2003; Heiser and Hebrok, 2004; Byrd and Grabel, 2004; Surace et al., 2006; abstracts enclosed as Exhibits 1-5). Briefly, these articles provide further support for the role for

hedgehog signaling articulated in the specification. Furthermore, these articles provide support for the use of agents that inhibit hedgehog signaling (e.g., hedgehog antagonists) for inhibiting vasculogenesis and angiogenesis. Inhibitors of vasculogenesis and/or angiogenesis can be used in the treatment of diseases including cancer and ocular neovascularization (See, Heiser and Hebrok, 2004 and Surace et al., 2006).

Nevertheless, to expedite prosecution, Applicants have amended claim 43 and added new claims 57-68 to more particularly point out certain embodiments of Applicants' invention. Specifically, the amended and newly added claims more particularly point out features of the hedgehog compounds used in the claimed methods, and also more particularly point out that the claimed methods are directed to inhibiting abnormally enhanced vascular growth in a subject. Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope.

On pages 5-12 of the Office Action, the Examiner advanced certain arguments that allegedly support the instant rejection. Applicants traverse and contend that the arguments are inapplicable to the amended claims.

On pages 5-6 of the Office Action, the Examiner raises concerns regarding the breadth of the phrase "enhanced vascular growth." Although Applicants do not acquiesce to any of the arguments on this point advanced in the instant Office Action, Applicants note that the amended claims more particularly point out that the claimed methods are directed to methods of inhibiting enhanced vascular growth. Applicants' amendment obviates the concerns articulated on pages 5-6 of the instant Office Action.

On pages 6-8 of the Office Action, the Examiner raises concerns regarding the breadth of hedgehog compounds for use in the claimed methods. Although Applicants do not acquiesce to any of the arguments on this point advanced in the instant Office Action, Applicants note that the amended claims more particularly point out the structural and functional attributes of hedgehog compounds within the scope of the present claims. Applicants' amendment obviates the concerns articulated on pages 6-8 of the instant Office Action.

On page 8 of the Office Action, the Examiner states that the claim encompasses "treatment of diseases associated with enhanced vascular growth wherein inhibition of angiogenesis is contrary to treatment of the disease." Applicants' amendments to the claims to

specify that the claims are directed to inhibiting enhanced vascular growth are believed to obviate this concern.

On pages 8-12, of the Office Action, the Examiner raises concerns with the breadth of selecting a "hedgehog compound capable of inhibiting the activity of a gene product expressed in an extraembryonic tissue." As a first point, Applicants note that, as amended, the claims are specifically directed to hedgehog compounds that inhibit hedgehog signaling (e.g., hedgehog antagonists). As such, the aspect of the rejection based on whether the identification and use of compounds that inhibit the activity of *any* gene produce expressed in an extraembryonic tissue is moot.

However, on pages 8-12 of the Office Action, the Examiner asserts that the specification does not provide sufficient guidance without undue experimentation "even if the gene product to be inhibited is Sonic hedgehog." Applicants respectfully disagree with this assertion. The specification and state of the art provided extensive guidance regarding the hedgehog signaling pathway and various compounds that can be used to inhibit hedgehog signaling. Furthermore, as noted above, the post filing art supports Applicants' position that the claims are enabled throughout their scope.

The Office Action appears to hinge enablement solely on predictability. It is true that the scope of enablement depends on the predictability of the relevant art. However, it is not required that the invention be restricted in scope to absolute black-and-white predictability. The test of enablement is whether one of skill in the art could practice the invention throughout its scope without undue experimentation – predictability and foreseeability are relevant only to the extent that undue experimentation is necessary to practice the full scope of the pending claims. However, the knowledge and technology available at the time of filing, permitted the preparation and testing of hedgehog antagonists, for example, blocking antibodies and variant polypeptides. The methods for making such antagonists were completely routine and the specification provided numerous in vitro models for testing whether particular compounds functioned as inhibitors of hedgehog activity (See, Examples). As such, the making and testing of hedgehog antagonists exemplifies "routine experimentation." While it is true that an "invitation to experiment" is not enough for patentability, if the invited experiments are merely routine, as here, no lack of enablement is present.

In view of the foregoing amendments and remarks, reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejection – 35 U.S.C. § 112, first paragraph, written description

Claim 43 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse this rejection and contend that the rejection is moot in view of the amended claims.

The Office Action cites several cases, such as *Fiers v. Revel*, *Amgen Inc. v. Chugai*, and *Fiddes v. Baird*, for the proposition that the compounds recited in the claims are not adequately described. These cases, however, are inapposite, because the claims considered in those applications were not method claims, as are the pending claims, but were directed to protein and nucleic acid sequences. “Possession”, as contemplated by the written description requirement, refers not to *physical* possession but to *conceptual* possession. The standard for measuring sufficiency of the written description, as articulated in *In re Gosteli*, 872 F.2d 1008 (Fed. Cir. 1989), was quoted in *Vas-Cath v. Mahurkar*, already cited by the Examiner:

A fairly uniform standard for determining compliance with the ‘written description’ requirement has been maintained throughout: ‘Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.’

While *Amgen v. Chugai* stands for the proposition that a nucleic acid is not conceived until the sequence is known, case law does not support the extension of this holding to method claims such as those presented by Applicants. Applicants are not aware of, nor does the Office Action cite, *any* cases holding that a *method* is not conceived until reduction to practice occurs.

The Office Action does not allege that the limitations and features of the claims are not literally supported by the specification. Methods are not subject to the doctrine of simultaneous conception and reduction to practice that applies when nucleic acids and proteins are claimed as compositions of matter. Instead, methods such as those claimed can be conceived independently and are constructively reduced to practice, at the very least, by the filing of a patent application. Applicants submit that the specification as filed fully supports Applicants’ conception of the subject matter of the pending claims at the time of filing of the present application as required by 35 U.S.C. § 112, first paragraph.

Nevertheless, to expedite prosecution, Applicants have amended claim 43 and added new claims 57-68 to more particularly point out certain embodiments of Applicants' invention. Specifically, the amended and newly added claims more particularly point out features of the hedgehog compounds used in the claimed methods, and also more particularly point out that the claimed methods are directed to inhibiting abnormally enhanced vascular growth in a subject. Applicants' amendments are not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 64-68 are means-plus-function claims. These claims are newly added as part of this response, and thus were not yet considered by the Examiner when making the instant rejection. However, Applicants note for the record that it is difficult to envision a set of circumstances under which it would be appropriate to reject means-plus-function claims as lacking sufficient written description. As is clear from the very language of the statute, claims interpreted under 35 U.S.C. § 112, sixth paragraph, are construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof. Thus, the claims are so intimately tied to the disclosure of the specification – for the specification lays the foundation for the scope of the claim in an intimate and inextricable manner – that the claims by definition must be adequately described. If an Examiner were to base a rejection on the equivalents that fall within the scope of the claim, Applicants direct the Examiner's attention to MPEP 2182: "The specification need not describe the equivalents of the structures, material, or acts corresponding to the means- (or step-) plus-function claims. See *In re Noll*, 545 F.2d 141, 149-50, 191 USPQ 721, 727 (CCPA 1976) ('The meaning of "equivalents" is well understood in patent law, ... and an applicant need not describe in the specification the full range of equivalents of his invention.' (citation omitted).")

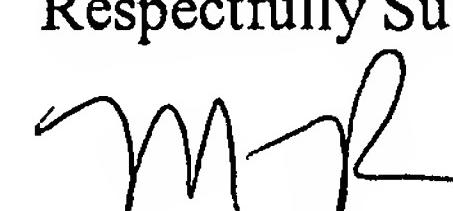
In view of the foregoing amendments and remarks, Applicants submit that the pending claims satisfy the written description requirement. Reconsideration and withdrawal of this rejection is requested.

CONCLUSION

If any clarification of the above response would facilitate prosecution of this application, Applicants respectfully request that the Examiner contact the undersigned at 617-951-7000. Should any further extension or other fee be required for timely consideration of this submission, Applicants hereby petition for same and request that the fee be charged to **Deposit Account No. 18-1945, under Order No. HUIP-P02-060.**

Respectfully Submitted,

Date: June 29, 2007



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Links

The morphogen Sonic hedgehog is an indirect angiogenic agent upregulating two families of angiogenic growth factors.

Pola R, Ling LE, Silver M, Corbley MJ, Kearney M, Blake Pepinsky R, Shapiro R, Taylor FR, Baker DP, Asahara T, Isner JM.

Department of Medicine, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts, USA.

Sonic hedgehog (Shh) is a prototypical morphogen known to regulate epithelial/mesenchymal interactions during embryonic development. We found that the hedgehog-signaling pathway is present in adult cardiovascular tissues and can be activated *in vivo*. Shh was able to induce robust angiogenesis, characterized by distinct large-diameter vessels. Shh also augmented blood-flow recovery and limb salvage following operatively induced hind-limb ischemia in aged mice. *In vitro*, Shh had no effect on endothelial-cell migration or proliferation; instead, it induced expression of two families of angiogenic cytokines, including all three vascular endothelial growth factor-1 isoforms and angiopoietins-1 and -2 from interstitial mesenchymal cells. These findings reveal a novel role for Shh as an indirect angiogenic factor regulating expression of multiple angiogenic cytokines and indicate that Shh might have potential therapeutic use for ischemic disorders.

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- ▶ Modulation of the angiogenesis response through Ha-ras control, placenta growth factor, and angiopoietin expression in mouse skin carcinogenesis. [Mol Carcinog. 2003]
- ▶ Angiopoietin-2, a natural antagonist for Tie2 that disrupts *in vivo* angiogenesis. [Science. 1997]
- ▶ Hypoxia-inducible factor-1 mediates activation of cultured vascular endothelial cells by inducing multiple angiogenic factors. [Circ Res. 2003]

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1: Circulation. 2003 Jul 29;108(4):479-85. Epub 2003 Jul 14.



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Postnatal recapitulation of embryonic hedgehog pathway in response to skeletal muscle ischemia.

Pola R, Ling LE, Aprahamian TR, Barban E, Bosch-Marce M, Curry C, Corbley M, Kearney M, Isner JM, Losordo DW.

Department of Medicine (Cardiovascular Research), St Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Mass 02135-2997, USA.

BACKGROUND: Hedgehog (Hh) proteins are morphogens regulating epithelial-mesenchymal signaling during several crucial processes of embryonic development, including muscle patterning. Sonic (Shh), Indian (Ihh), and Desert (Dhh) hedgehog constitute the repertoire of Hh genes in humans. The activities of all 3 are transduced via the Patched (Ptc1) receptor. Recent observations indicate that exogenous administration of Shh induces angiogenesis. Here, we studied whether the endogenous Hh pathway, in addition to its functions during embryogenesis, plays a physiological role in muscle regeneration after ischemia in adults. **METHODS AND RESULTS:** We found that skeletal muscle ischemia induces strong local upregulation of Shh mRNA and protein. In addition, the Ptc1 receptor is activated in interstitial mesenchymal cells within the ischemic area, indicating that these cells respond to Shh and that the Shh pathway is functional. We also found that Shh-responding cells produce vascular endothelial growth factor under ischemic conditions and that systemic treatment with a Shh-blocking antibody inhibits the local angiogenic response and the upregulation of vascular endothelial growth factor. **CONCLUSIONS:** Our study shows that the Hh signaling may be recapitulated postnatally in adult and fully differentiated muscular tissues and has a regulatory role on angiogenesis during muscle regeneration after ischemia. These findings demonstrate a novel biological activity for the Hh pathway with both fundamental and potential therapeutic implications.

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- ▶ Sonic hedgehog signaling plays an essential role during embryonic salivary gland epithelial branching morphogenesis. [Dev Dyn. 2004]
- ▶ Targeted expression of SHH affects chondrocyte differentiation, growth plate organization, and Sox9 expression. [J Bone Miner Res. 2004]
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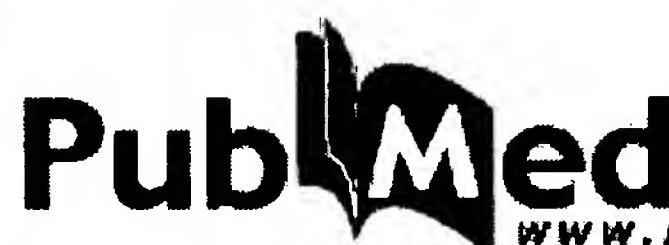
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Development and cancer: lessons learned in the pancreas.

Heiser PW, Hebrok M.

Diabetes Center, Department of Medicine, University of California, San Francisco, California 94143, USA.

Cancer progression and organ development are similar phenomena. Both involve rapid bursts of proliferation, angiogenesis, tissue remodeling, and cell migration. Therefore, it is not surprising that both processes utilize similar signaling machinery. In fact, many recent studies have suggested that cancer is a disease triggered by the erroneous re-activation of signaling pathways that are typically downregulated after the completion of embryonic development. This link between embryonic development and cancer is particularly exciting because it suggests that we might be able to exploit the knowledge gained in studies of Developmental Biology to obtain novel insights into tumor biology. Our evolving understanding of pancreatic adenocarcinoma is an excellent example of this relationship between development and cancer. Here we discuss recent studies that have indicated important roles for two major developmental signaling pathways in pancreatic cancer: Notch and Hedgehog (Hh).

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Hedgehog signaling in murine vasculogenesis and angiogenesis.

Byrd N, Grabel L.

Department of Pediatrics and Cell Biology, 326 Nanaline Duke Bldg., Box 3179, Duke University Medical Center, Durham, North Carolina, USA.

Vasculogenesis-the formation of blood vessels de novo from endothelial cells-and angiogenesis-the process of blood vessel remodeling-are regulated by a number of signal transduction pathways, some specific to the vascular system and others used more broadly during embryogenesis. Recent evidence in both zebrafish and mouse suggests a role for Hedgehog (Hh) signaling in both vasculogenesis and angiogenesis. Hh signaling can target endothelial cells directly or can stimulate blood vessel support cells to produce vascular growth factors. Current studies are aimed at determining how the Hh cascade interacts with the other signaling pathways to promote vessel differentiation.

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- ▶ Role of the vascular endothelial growth factor isoforms in retinal angiogenesis and DiGeorge syndrome. [Development Genes and Evolution. 2005]
- ▶ Hedgehog signaling is required for adult blood stem cell formation in zebrafish embryos. [Dev Cell. 2005]
- ▶ Vasculogenesis. [Annu Rev Cell Dev Biol. 1995]

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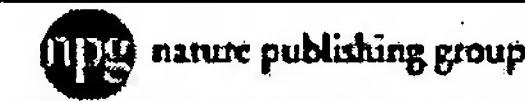
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Inhibition of ocular neovascularization by hedgehog blockade.

Surace EM, Balaggan KS, Tessitore A, Mussolini C, Cotugno G, Bonetti C, Vitale A, Ali RR, Auricchio A.

Telethon Institute of Genetics and Medicine, 80131 Naples, Italy;
S.E.M.M. - European School of Molecular Medicine - Naples site, Italy.

Ocular neovascularization associated with proliferative diabetic retinopathy and age-related macular degeneration is the leading cause of severe visual loss in adults in developed countries. Physiological and pathological retinal angiogenesis may occur independently in postnatal life through the complex activation of pro- and antiangiogenic pathways. We report that the Sonic hedgehog (Shh) pathway is activated in the retina in animal models of retinal and choroidal neovascularization. We show that pharmacological inhibition of the Shh signaling pathway significantly reduces physiological retinal angiogenesis and inhibits pathological vascularization in both models. Under retinal hypoxic conditions, inhibition of the Shh pathway results in reduction of vascular endothelial growth factor (VEGF) level, along with that of Patched-1 (Ptch1), a canonical Shh target, thus placing Shh activation upstream of VEGF in experimental retinal neovascularization. Our data demonstrate the requirement of the Shh pathway for retinal angiogenesis and its inhibition as a potential therapeutic strategy targeting ocular neovascular disease.

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- ▶ Inhibition of platelet-derived growth factor B signaling enhances the efficacy of anti-vascular endothelial growth factor therapy in multiple models of ocular neovascularization. [Am J Pathol. 2006]
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